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Recognition of Leukemia in Skeletal Remains: Report and Comparison of Two Cases

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ABSTRACT Recognition of disease in the archeologic record is facilitated by characterization of the skeletal impact of documented (in life) disease. The present study describes the osteological manifestations of leukemia as identified in the skeletons of two individuals diagnosed during life: a 3-year-old black girl with acute lymphocytic leukemia and a 60-year-old white male with acute myelogenous leukemia in the Hamann-Todd collection. Contrasting with the lack of specificity of radiologic findings, macroscopic skeletal changes appear sufficiently specific to allow distinguishing leukemia from other forms of cancer. While leukemia appears confidently diagnosable, distinguishing among the varieties (e.g., myelogenous and lymphocytic) does not appear possible at this time. Skeletal findings in leukemia are presented in tabular form to facilitate their application to future diagnosis of the disease in the archaeological record. Am J Phys Anthropol 102:481–496, 1997.

Most textbooks of paleopathology (e.g., Steinbock, 1976; Ortner and Putschar, 1981; Zimmerman and Kelley, 1982; Rothschild and Martin, 1993) devote only a few lines to leukemia, assuming the lack of specificity of findings. This perspective derived from medical x-rays (Thomas et al., 1961; Rogalsky et al., 1986), which do not appear to allow leukemia, metastatic cancer, and fungal infection to be confidently distinguished.

Leukemias are cancers of myeloid or lymphoid cell lines. Leukemia is more common in children (than adults), who are also more prone to exhibit skeletal changes (more than 60% of afflicted individuals) (Thomas et al., 1961; Silverstein and Kelly, 1963; Nixon and Gwinn, 1973). Increased incidence of osseous involvement was found in children under 4 years of age (Nixon and Gwinn, 1973). The incidence of childhood leukemia is four cases/100,000 children (Gallagher et al., 1991), with most cases aged 2–5 years (Gallagher et al., 1991; Nixon and Gwinn, 1973; Willson, 1959).

Leukemia bone involvement was first illustrated in 1901 (von Jaksch, 1901), only a few years after the technique (x-ray) was first discovered. This was 56 years after Virchow's original description of leukemia in 1845 (Simmons et al., 1968). The current study was initiated to describe in detail the

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osseous impact of leukemia, to compare and contrast juvenile (lymphocytic) with adult (myelocytic) leukemia, and to identify any characteristics which might facilitate differential diagnosis.

MATERIALS AND METHODS

Two individuals with leukemia diagnosed in life were identified in the Hamann-Todd human skeletal collection, which is housed at the Cleveland Museum of Natural History. Childhood acute lymphocytic leukemia was present in the skeleton (HTH 1115) of a 3-year-old black female and acute myelogenous leukemia in that of a 60-year-old white male (HTH 2721). The skeletons were complete, with all epiphyses present in the child. Macroscopic examination of the skeletons was performed, especially noting changes in calvarial bones (external and internal aspects), facial architecture and sinuses, long bones, vertebrae, and ribs. Autopsy x-rays were compared to those taken of isolated bones.

The term *fronts of resorption* will repeatedly appear in the description of the bony lesions associated with leukemia. Although this term was originally used to describe erosive lesions in rheumatoid arthritis (Leisen et al., 1987), it also appears to characterize the changes observed in leukemia (both disorders are associated with biologic resorptive processes). The term refers to cellular resorptive processes produced by synovial and osteoclastic cell overgrowth. These processes result in a smooth, continuous area (front) of bone resorption.

TABLE 1. Summary of macroscopic skeletal findings in leukemia

Macroscopic observations	Acute lymphocytic	Acute myelocytic
Ectocranial pitting		
Pit basilar foramen	+	−
Pit periosteal reaction	+	−
Orbital	−	−
Temporal	−	−
Frontal-parietal parallel lesions	+	−
Occipital	+	−
Base around foramen magnum	+	+
Sphenooccipital clivus	+	+
Endocranial pitting		
Crenulation	+	−
Dendritic excavation	+	−
Orbital	−	−
Temporal	+	−
Frontal	+	−
Occipital	+	−
Cranial fossae	−	−
Spenooccipital clivus	+	−
Holes along sagittal sinus	+	−
Maxillary discoloration	+	−
Periosteal reaction		
Mandible	−	+
Long bones	+	+
Ribs	−	+
Vertebrae	−	+

RESULTS

Childhood leukemia

Almost all elements of the skeleton exhibited pronounced osteological changes (Table 1). These changes are described below by anatomical region.

The skull. The skull and teeth were normal in size and shape. All sutures were open and calvarial bone thickness normal. Marked ectocranial pitting (0.1–2.0 mm in diameter) was especially prominent on the posterior and suprasquamosal (suture) aspects of the parietals, the superior aspect of the occipital, superior temporal line, glabella, and central aspects of the frontal (Fig. 1). Facial (except the roof of the orbits) bones, temporal bones, and the base (prosthion to inion) of the skull were generally spared. Inferior frontoparietal pits were aligned in two parallel, horizontal rows: one followed the superior temporal line while the second was suprasquamosal (Fig. 2).

The pits were superficial, rarely penetrating the external diploic plate. Approximately half of the pits appeared as holes with smooth, minimally remodeled edges. The other half resembled the fronts of resorption seen in rheumatoid arthritis (Leisen et al., 1987; Rothschild et al., 1987, 1990) but with different distribution (not affecting joints). These fronts of resorption often coalesce (especially in the glabella and posterior parietal regions), although retaining recognizable individual identity. A small foramen (often off-center) was identified at the base of approximately 70% of pits, independent of variety.

Focal periosteal reaction was noted in the posterior aspect of the parietal, predominantly affecting the area around smooth hole–appearing pits (Fig. 1). This periosteal reaction was minimally raised and slightly

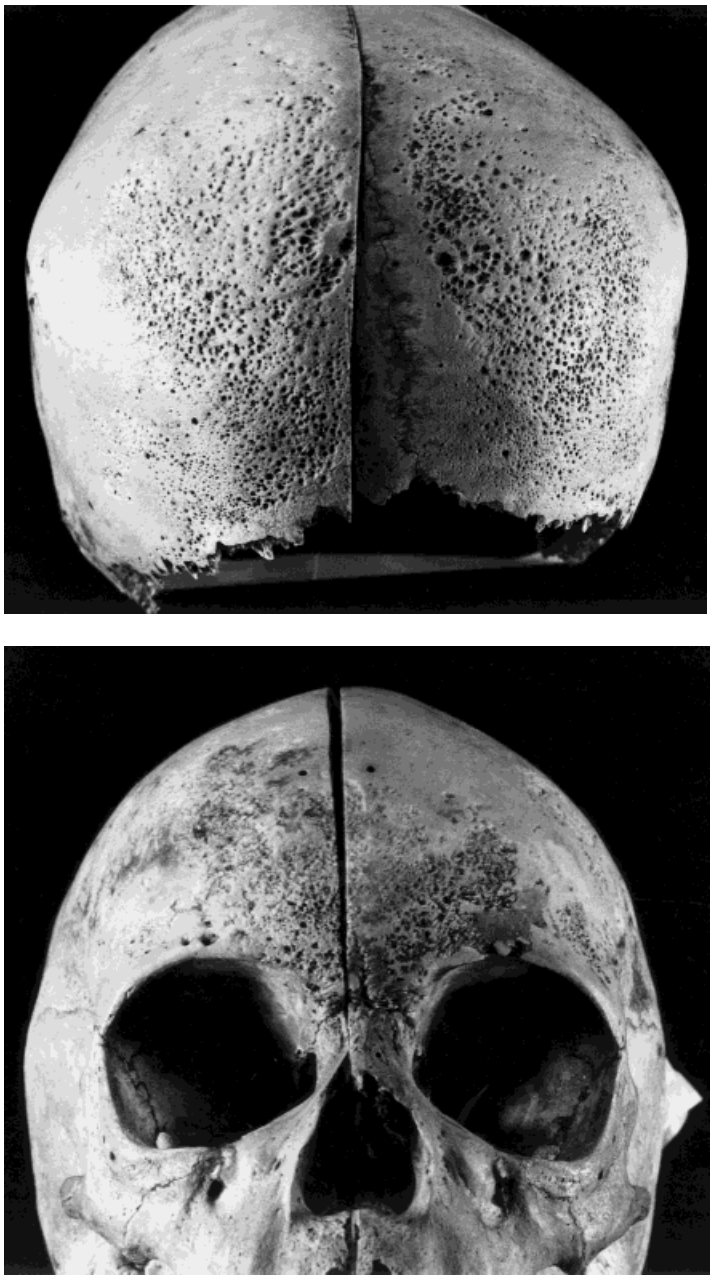

Fig. 1. Posterior (**top**) and anterior (**bottom**) views of skull (HTH 1115). Marked ectocranial pitting (0.1–2.0 mm in diameter) on posterior parietal and supraglabellar regions. Focal periosteal reaction at posterior aspect of the parietals.

discolored. Focal bone resorption was noted in the external diploic plate of the parietal.

Endocranial involvement was more generalized, although quite different in character from what was observed on the ectocranium. The orbital roof (frontal), middle, and posterior cranial fossae were spared. Although pits were present endocranially (in a very limited distribution), most of the endocranial changes were superficial and had a crenulated (à la Tobias, 1991) in appearance. Curiously, the distribution of endocranial lesions (both crenulated and periosteal) was essentially the converse of what was

Fig. 2. Lateral view of skull (HTH 1115). Two parallel, horizontal rows of pits following superior temporal and suprasquamosal lines, in addition to frontoparietal pitting.

Fig. 3. Endocranial view of skull (HTH 1115). Crenulated areas contiguous with branching excavations, sharply undercutting the endocranial surface, resulting in a dendritic root appearance.

observed on the ectocranial surface. The only exceptions were holes with smooth, minimally remodeled edges distributed along a half-centimeter thick, suprasquamosal line and overlying the most posterior portion of the sagittal sinus. The crenulated areas were contiguous with the branching excavations (Fig. 3). The latter sharply undercut the endocranial surface, resulting in a dendritic root appearance.

Mild pitting (both varieties) was present on the external surface of the nasals and frontal process of the zygomatic bone. Confluent involvement was noted in the inferior aspect of the orbital roof and superior orbital rim. While discoloration was noted on the maxillary part of the face, no periosteal reaction was recognized in this area. The mandible was normal in size and shape. Mild periosteal reaction was present on the external surface of the right ascending ramus.

Lateral radiographs revealed mild frontal intradiploic plate tunneling and an unusual pattern of generalized bone resorption (Fig. 4; Table 2). The latter uniformly involved the skull but with only limited temporal bone involvement. There was minimal disruption of the ectocranial surface of the external diploic space. The internal diploic plate appeared intact. Frontal and facial bone resorption resulted in a parallel arrangement of residual trabeculae (Fig. 4). The appearance resembled a swept-back coiffeur. A centrifugal pattern of bone resorption was noted in the midparietal, presenting a sunburst appearance of bone resorption. That was surrounded by generalized (but without orientation) microfoci of bone resorption. Fronts of resorption in the temporal bone were noted in addition to the branched pattern.

Shoulder girdle and upper limb bones. Pits (holes) were present on the dorsal aspect of the right acromial head of the clavicle and posteriolateral margin. The latter were associated with minimal periosteal reaction. Large pits (with fronts of resorption) were present on the ventral aspect of the scapula and along the vertebral and glenoid borders (Fig. 5). Large fronts of bone resorption were present along the glenoid border, the entire inferior aspect of the scapular spine, and infraspinatus fossa (sparing the peripheral half centimeter and central centimeter of that fossa).

The humeral epiphyses were normal. Multiple pits (fronts of resorption) were located in the anterior aspect of the distal humeral metaphyses. Large pits (fronts of resorption) were present in the proximal ulnar and distal right radial metaphyses. Mild periosteal reaction was present along the proximal ulnar diaphyses. Multiple diaphyseal and metaphyseal pits (fronts of resorption) were present in metacarpals, predominantly affecting the ventrolateral aspects. Proximal

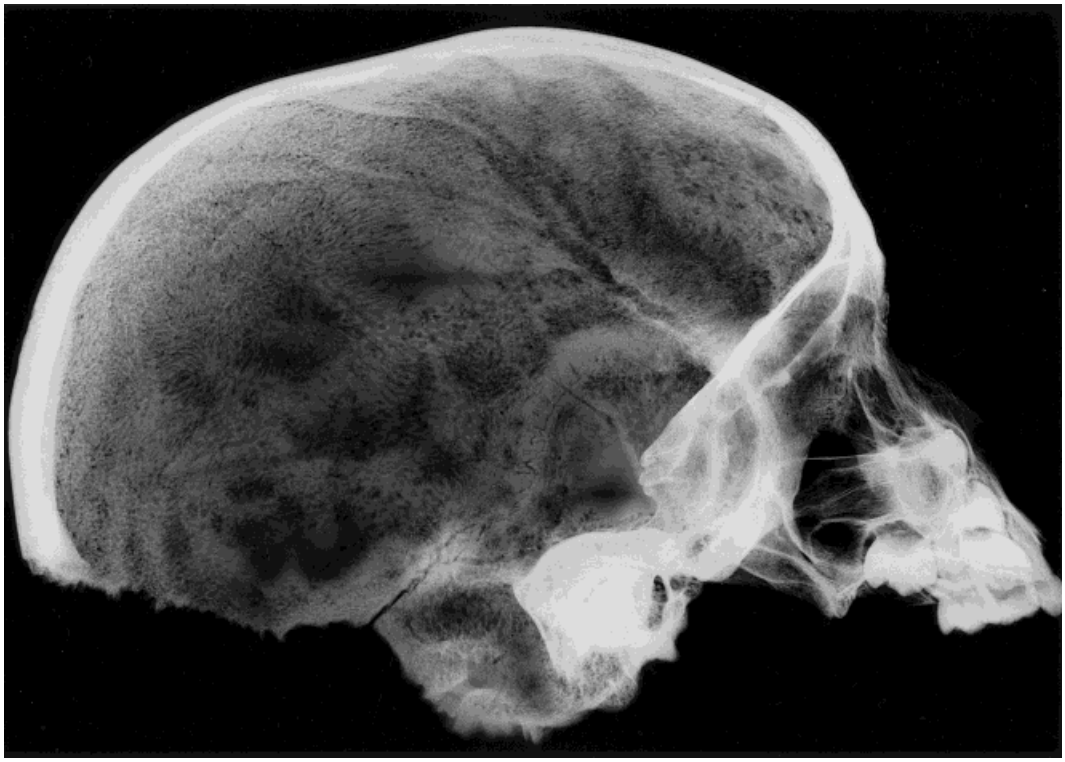

Fig. 4. Lateral skull (HTH 1115) radiograph. Mild frontal intradiploic plate tunneling. Generalized bone resorption with minimal disruption of internal diploic plate. Parallel arrangement of residual trabeculae, producing swept-back coiffeur appearance.

TABLE 2. Radiologic skeletal findings in leukemia

Radiologic observations	Acute lymphocytic	Acute myelocytic
Intracortical resorption	+[1–3]	−[1–3]
Parallel trabeculae	+[2,4,5]	−[3,5]
Centrifugal pattern	+[3,6,7]	−[3,7]
Microfoci	+[1,5,6,8]	+[1,5,8–10]
Metaphyseal bands	Common[1,3,6,11–14]	Rare[1,3,11,12,15]
Tibia/fibula predominance	+[8,11,16]	−[8,11,16]
Endosteal scalloping	+[1,8]	−[1]
Gouty erosions	Occur[17]	Occur[17]

[1] Silverstein and Kelly, 1963.
[2] Simmons et al., 1968.
[3] Thomas et al., 1961.
[4] Kalayjian et al., 1946.
[5] Nixon and Gwinn, 1973.
[6] Willson, 1959.
[7] Spilberg and Meyer, 1972.
[8] Gallagher et al., 1991.
[9] von Jaksch, 1901.
[10] Rogalsky et al., 1986.
[11] Baty and Vogt, 1935.
[12] Iversen, 1966.
[13] Gruenebaum and Salinger, 1967.
[14] Rosenfield and McIntosh, 1977.
[15] Pear, 1974.
[16] Benz et al., 1976.
[17] Resnick and Niwayama, 1988.

phalanx involvement was generally limited to holes in the ventral aspect of the proximal diaphyses, while middle and distal phalanx involvement was predominantly limited to the distal diaphyses. Vascular foramina were enlarged.

Radiologic examination of the humerus revealed endosteal and intracortical bone resorption, most prominent in the distal diaphyses. Linear transcortical lines (vascular foramina) were also prominent. Two millimeter wide, radiolucent bands were located approximately 3 mm from the proximal epiphyses.

Lower limb bones. Large coalescing fronts of resorption were present in the distal femoral metaphyses, in contrast to holes in the central trochanteric region and central condylar portion of the distal epiphyses. Minimal periosteal reaction was present on the femoral diaphyses.

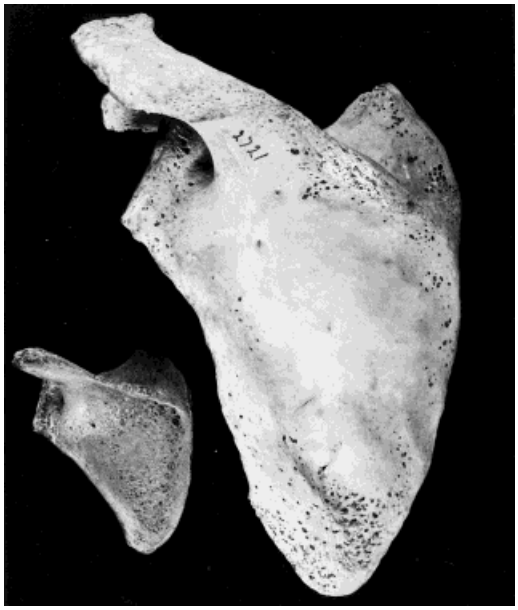

Fig. 5. Posterior view of scapulae (juvenile, lymphocytic leukemia, HTH 1115; adult, myelocytic leukemia, HTH 2721). Large pits (with fronts of resorption) along the vertebral and glenoid borders, inferior aspect of scapular spine, and inferior part of infraspinatus fossa.

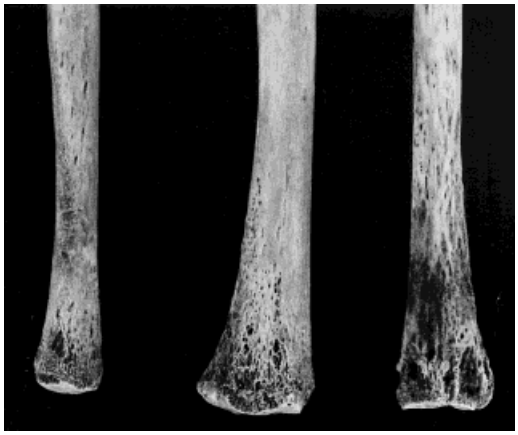

Fig. 6. Anterior view of distal fibula (right), radius (middle) and ulna (left) (HTH 1115). Generalized diaphyseal and metaphyseal pitting (fronts of resorption).

The osteological changes in the tibiae and fibulae were the most extensive of the postcranial lesions. Generalized diaphyseal and metaphyseal pitting (fronts of resorption) spared only the lateral aspect of the tibia, while the fibulae were diffusely affected (Fig. 6). Linear oval defects (1–3 mm in length, 1–2 mm wide, 0.3–0.8 mm depth), with sharply defined borders, were present throughout the fibulae. Holes were present in the intercondylar area of the tibia. Tibial and fibular periosteal reaction was diaphyseal in distribution.

Fronts of resorption were diffusely present in metatarsal diaphyses and metaphyses and, as an isolated phenomenon, in phalangeal diaphyses. A large marginal erosion was present on the talar aspect of the tibio-talar joint (Fig. 7). Minimal reactive new bone formation accompanied this "mass-effect" lesion. The appearance was identical to that reported with space-occupying masses of gout (Rothschild and Heathcote, 1995). Focal fronts of resorption and holes were noted on the medial aspect of the talus and medial cuneiform. Diffuse fronts of resorption and periosteal reaction were noted on the calcaneus.

X-rays of the femur revealed sclerotic lines, paralleling the distal and proximal metaphyses. Mild endosteal scalloping and slight intracortical resorption were present. Alternating juxtaepiphyseal osteopenic and sclerotic bands were noted in the distal and proximal tibial metaphyses (Fig. 8). Intracortical resorption, endosteal scalloping, and periosteal new bone formation were present in tibiae and fibulae. Generalized osteopenia with focal linear resorption was present in the metatarsals (Fig. 9). An erosion with slightly sclerotic margin was present in the tarsal component of the tibio-tarsal joint.

Thoracic cage. Extensive fronts of resorption were present on the sternum, predominantly affecting the posterior surface. Fronts of resorption were present, in a linear distribution, at the inferior and superior internal borders of all ribs.

All vertebrae were affected (Fig. 10). Pitting, in the form of holes, predominantly affected the anterior portion of the body of the cervical vertebrae, with minimum involvement of spinous and transverse process. Diffuse pitting of thoracic vertebrae spared only the articular surfaces, end plates, and internal aspect of the neural arch. The most severely affected axial region was the posterior aspect of the lumbar vertebrae. While pitting was predominantly in the form of holes in the more cephalic tho-

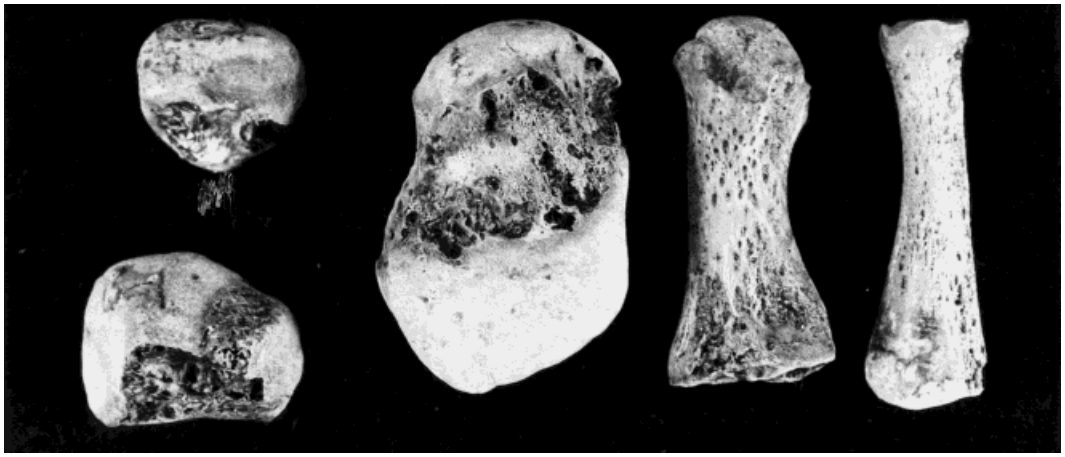

Fig. 7. Superior view of tarsals and metatarsals (HTH 1115). Mass-effect lesion producing large marginal erosions with minimal reactive new bone formation on tarsals. Permeative fronts of resorption in metatarsals.

racic vertebrae, fronts of resorption were present in the more caudal thoracic and lumbar vertebrae. Thoracic and lumbar anterior vertebral concavity was accentuated.

Lateral radiographs of thoracic and lumbar spine revealed demineralization and accentuated, often V-shaped, anterior vertebral body concavity.

The pelvis. Pitting (both holes and fronts of resorption) were present on the alae and anterior aspect of the sacrum. Superficial bone resorption was present along both internal and external margins of the more posterior part of the superior iliac crest. Holes and fronts of resorption were seen on the ischium and pubic bones.

X-rays revealed focal lytic areas at the epiphyseal margin of the iliac crest (Fig. 11).

Adult leukemia

The osteological expression of leukemia in the adult skeleton was very similar in character to that observed in the juvenile skeleton, differing predominantly in distribution (Table 1).

The skull. Cranial osteological changes were limited to the sphenooccipital clivus, where marked pitting and large resorptive areas were present. This contrasted with advanced osteological changes in the mandible. Erosions were present in a marginal distribution around both condyles (Fig. 12), predominantly affecting the posterior aspect. There was no evidence of reactive new bone formation. Numerous large and small holes were present in the anatomical "gutter" leading to the mandibular foramen, while only small, shallow holes were present in the anterior aspect of the posterior part of the mandibular body. All teeth had been lost during life. The medial aspect, stretching from the inferior coronoid process to the mental foramen, was pitted with isolated fronts of resorption without evidence of reactive new bone formation. Confluently distributed, 1 mm discrete lytic areas were predominantly frontal and parietal in (radiologic) distribution.

The upper limb. Numerous, deeply penetrating holes of irregular size and shape were present on the inferior aspect (especially the acromial head) of the clavicle. Isolated holes were present in a linear distribution along the shaft and around the sternal head. While holes were the predominant lesion along the dorsal surface, fronts of resorption dominated the ventral surface. Marginal erosions were present at the acromio-clavicular joints, with no reactive new bone formation.

Large pits (fronts of resorption) were present along the vertebral and glenoid borders

Fig. 8. Anterior-posterior radiograph of proximal tibia (HTH 1115). Alternating juxtaepiphyseal osteopenic and sclerotic bands. Intracortical resorption, endosteal scalloping, and periosteal new bone formation.

of the ventral aspect of the scapulae (Fig. 5). Large fronts of resorption were present along the glenoid border, the entire inferior aspect of the scapular spine, and the infraspinatus fossa (sparing only the peripheral half centimeter and central centimeter of that fossa). Small marginal erosions were present at the gleno-humeral and acromio-clavicular joint, with no evidence of reactive new bone formation.

The humeral shaft and distal epiphysis were unaffected, except for a few small, isolated pits. Enlarged vascular channels were present in the humeral metaphyses in the surgical and anatomical neck regions. Radius, ulna, hand, and foot bones were not affected.

Radiographs of the long bones revealed osteopenia and a mild permeative resorptive pattern but no metaphyseal bands (Table 2).

The lower limb. The femoral shaft and distal epiphysis were unaffected. The proximal metaphyses (especially the femoral neck and intertrochanteric regions) were perforated by numerous large holes (Fig. 13). Linear fronts of resorption were present around the lesser trochanter. Minimal linear periosteal reaction was present at the anterior aspect of the proximal metaphyses. Tibia and fibula were not affected. A subperiosteal ossified hematoma was present on the diaphysis of the second right metatarsal. Marginal erosions with reactive new bone (forming an overhanging edge) were present in the right navicular and first metatarsal. The "space-occupying" appearance of the latter was characteristic of gout.

Radiographs of the long bones revealed osteopenia and a mild permeative resorptive pattern but no metaphyseal bands. Well-defined lytic areas were noted in the femoral neck (Fig. 14).

The thoracic cage. The sternum (both body and manubrium) were heavily perforated (on both sides). The ribs were perforated linearly along their superior margins and subcostal groove (Fig. 15).

Radiologic evaluation revealed endosteal scalloping and intracortical resorption, with a permeative pattern. Isolated periosteal reaction was noted in areas of cortical expansion. Radiologic evidence of periosteal elevation was limited to areas where intracortical resorption was prominent.

All vertebrae were affected, although with variable distribution and periosteal reaction (Fig. 16). Holes and fronts of resorption were present predominantly in the posterior and lateral elements (including pedicles) of the cervical and sacral vertebrae. This contrasted with predominant involvement of the bodies of thoracic and lumbar vertebrae (sparing the pedicles). Macroscopic cervical involvement was distributed to the inferior aspect of the spinous processes and posterior aspect of the bodies. Most lesions were of

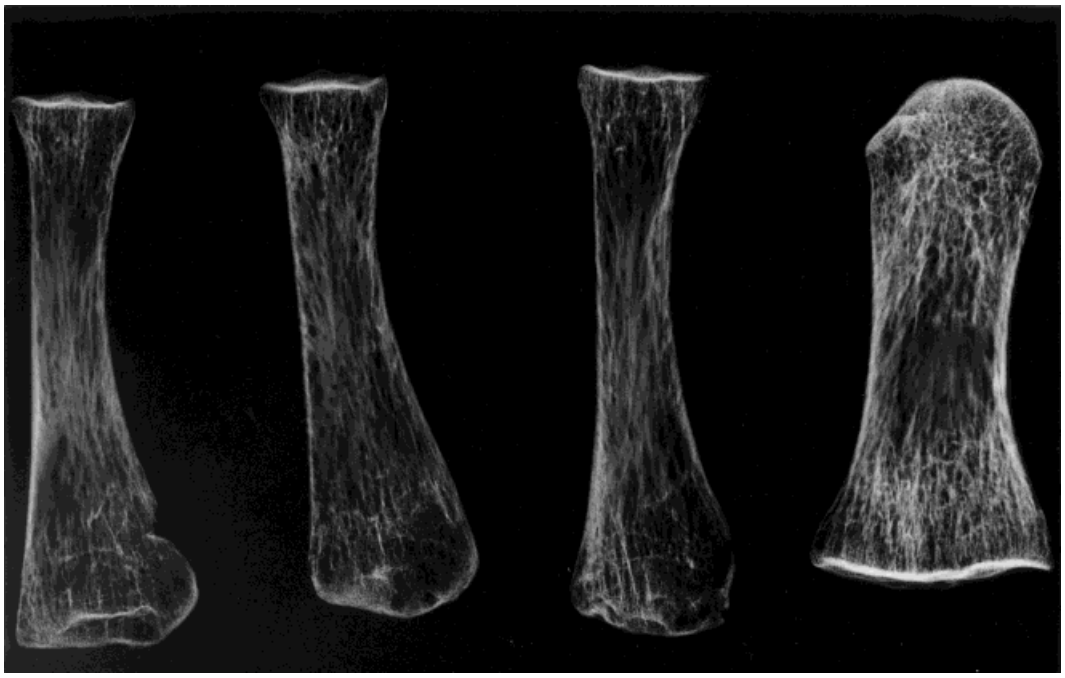

Fig. 9. Anterior posterior x-ray of metatarsals (HTH 1115). Generalized osteopenia with focal linear resorption.

relatively uniform size (0.1–0.2 mm) with only isolated areas of coalescence (i.e., an elongated 0.5 × 2 cm lesion in the sacrum and spherical lesions in the body of T10 and the spinous process of T3; 0.5 cm and 0.7 cm in diameter, respectively). Mild anterior periosteal reaction was noted in the fifth lumbar vertebra, associated with mild lateral vertebral compression (? fracture).

Radiographic examination revealed permeative lesions of thoracic spinous processes.

The pelvis. Pitting (both holes and fronts of resorption) was present on the alae, especially along internal and external margins of the more posterior part of the superior iliac crest (Fig. 17). Holes and fronts of resorption were also present on the ischium and pubic bones. Linear periosteal reaction was noted along the superior and medial aspects of the transverse processes of the sacrum. Radiographs (Fig. 18) revealed solitary and coalescing (1–3 mm) lytic areas in the ischium, pubic and ilium, sparing only central most aspect of the latter.

DISCUSSION

The macroscopic and radiologic changes in two individuals with leukemia (diagnosed in life) are delineated herein. From the paleopathology perspective, three issues seen pertinent: 1) whether the bony changes are sufficiently characteristic to allow confident diagnosis of leukemia, 2) whether bony changes are sufficient to distinguish between the different types of leukemia, and 3) whether the variation noted above is a manifestation of variety of leukemia or simply age-dependent bone susceptibility/responsiveness.

Are bony changes sufficiently characteristic for confident diagnosis of leukemia?

Radiologic. Although x-ray changes are not pathognomonic for leukemia (Rogalsky et al., 1986; Resnick and Niwayama, 1988), the most characteristic changes are transverse radiolucent metaphyseal bands (Silverman, 1948). Present in 10–89% of childhood

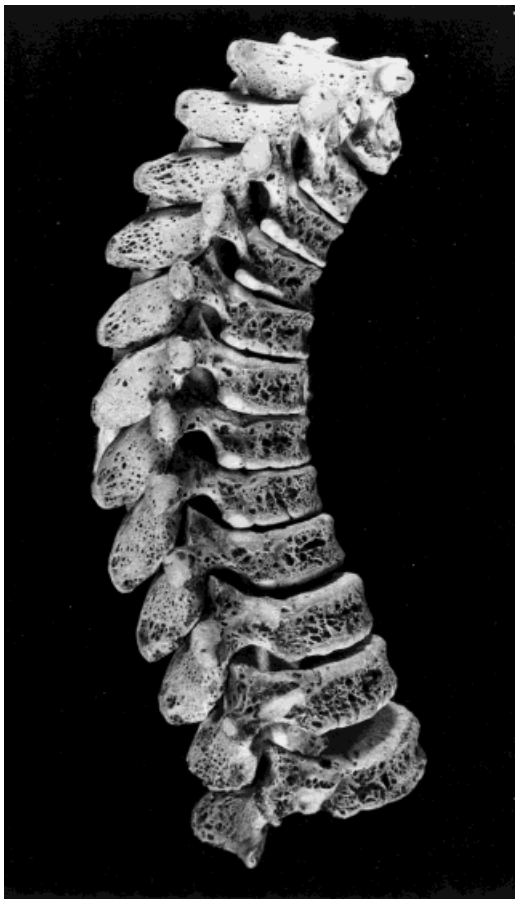

Fig. 10. Lateral view of thoracic vertebrae (HTH 1115). Diffuse pitting.

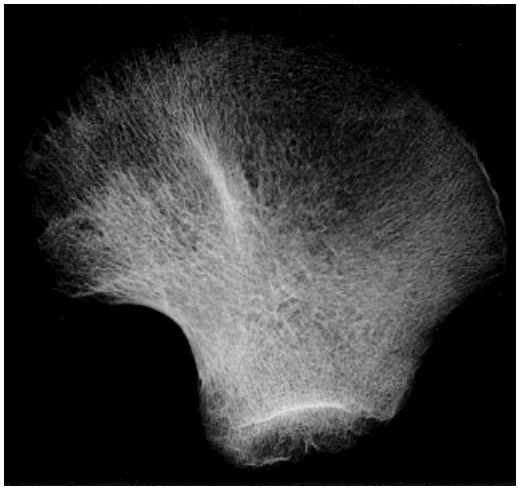

Fig. 11. Anterior-posterior x-ray view of inominate (HTH 1115). Focal lytic areas at epiphyseal margin of iliac crest.

Fig. 12. Posterior-superior view of mandibular condyles (HTH 2721). Marginal erosions.

leukemia and 7% of adult leukemia (Silverman, 1948; Simmons et al., 1968; Thomas et al., 1961; Pear, 1974), they are especially prominent at sites of rapid growth (proximal tibia, distal femora, distal radius, and distal ulna) (Tables 2, 3). These 2–15 mm wide bands (Fig. 8) have "well-defined margins, but without so-called 'penciled in' sharpness, as if a zone of bone had been erased beneath a thin metaphyseal shell" (Willson, 1959). They are localized parallel and adjacent to epiphyseal and apophyseal margins (e.g., ilium, ischium, vertebral end plates) (Baty and Vogt, 1935) and even to costochondral junctions (Thomas et al., 1961; Benz et al., 1976). The latter are distinguishable from scurvy (in which costochondral junctions are enlarged) and rickets (in which they develop a cupped, splayed appearance) (Gruenebaum and Salinger, 1967).

Simmons et al. (1968) suggested that metaphyseal bands are nonspecific below age 7. Although they have also been reported in scurvy, bacteremia, cerebellar neoplasm, brain abscess, healing rickets, congenital syphilis, and juvenile rheumatoid arthritis (Willson, 1959; Simmons et al., 1968), their occurrence in those disorders apparently is quite rare. Among 740 individuals with such metaphyseal bands, only 32 had diagnoses other than leukemia (Willson, 1959). Speci-

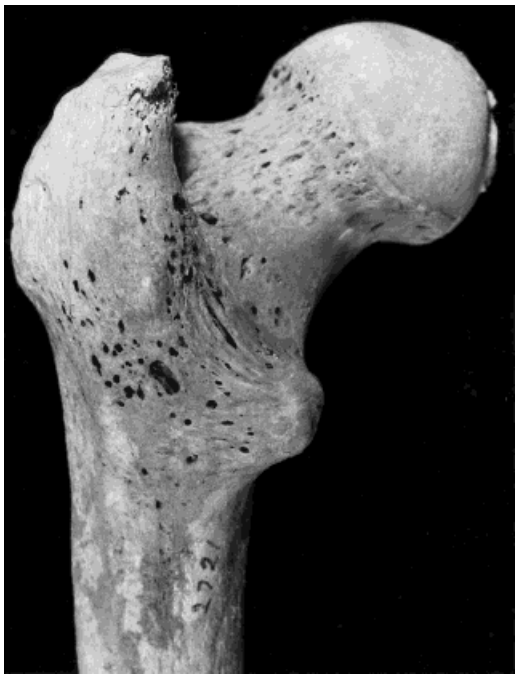

Fig. 13. Posterior view of proximal femur (HTH 2721). Numerous large holes perforate the femoral neck and intertrochanteric regions.

ficity appears significantly greater after age 2, as only four individuals in that group did not have leukemia.

Osteolysis is the other major radiologic finding in leukemia, reported in 30% of children and 39% of adults with leukemia (Silverman, 1948; Silverstein and Kelly, 1963; Simmons et al., 1968). Focal areas of trabecular radiolucency (Figs. 8, 9, 11, 14, 18) may be sharply or ill-defined or even "moth-eaten" in appearance, occasionally associated with endosteal resorption. "Conglomeration of such lesions" may produce a diffuse osteolytic appearance (Silverman, 1948).

Radiologic findings (Tables 2, 3), while suggestive, are not pathognomonic. As the presence of metaphyseal bands has not been reported in metastatic cancer, they may be helpful in distinguishing leukemia and metastatic cancer. With that exception, the radiologic appearance of leukemia and metastatic cancer may not sufficiently differ to allow differential diagnosis.

While the sunburst resorption pattern is not specific for leukemia (Resnick and Niwayama, 1988), the significance of the swept-back coiffeur pattern of residual cranial trabeculae (Fig. 4) is unclear. While it appears unique, the possibility of an artifact (related to the absence of soft tissues) must be considered.

Macroscopic. Two forms of lytic lesions with basilar foramina (70%) were noted in the patients with leukemia (Figs. 1, 6, 10, 13, 15–17). Approximately half the lytic lesions appeared as holes, with smooth, minimally remodeled edges. The other half resembled the fronts of resorption seen in rheumatoid arthritis (Leisen et al., 1987; Rothschild et al., 1987, 1990) but with a different distribution (not affecting joints). While the fronts of resorption often coalesced, the component lesions always maintained their individual identity. Minimal periosteal reaction occasionally accompanied the former lesions. The lytic lesions (fronts of resorption) and holes were easily distinguished from the space-occupying mass lesions of metastatic cancer. Permeative lesions (e.g., rib) may be found in both leukemia and metastatic cancer (Resnick and Niwayama, 1988; Rothschild and Martin, 1993) and thus appear nonspecific.

It is unclear if the crenulated areas (contiguous with branching endocranial excavations) (Fig. 3), parallel rows of ectocranial frontal parietal pits (Fig. 2), and the accentuated, often V-shaped anterior vertebral body concavity have diagnostic implications for leukemia, although they were unique to our experience (Table 1). Demineralization was a nonspecific finding.

Gout, a known complication of hyperplastic diseases (including leukemia) (Resnick and Niwayama, 1988; Rothschild and Martin, 1993), was recognized (Fig. 7) in the examined skeletons. Space-occupying mass appearing marginal joint erosions, with or without an overhanging edge, were thought diagnostic (Rothschild and Heathcote, 1995). The possibility exists that the lesion attributed to gout in the 3-year-old with leukemia may not have been gout. However, its identical appearance to that of the adult lesion and to the rather unique nature of some gouty lesions in adults (Rothschild and Heathcote, 1995) makes diagnosis likely.

Fig. 14. Anterior-posterior x-ray view of proximal femur (HTH 2721). Osteopenia and focal femoral neck lytic areas with slight superior periosteal reaction. Postmortem diaphyseal crack is incidently noted.

Fig. 15. Internal view of ribs (HTH 2721). Linearly distributed perforations.

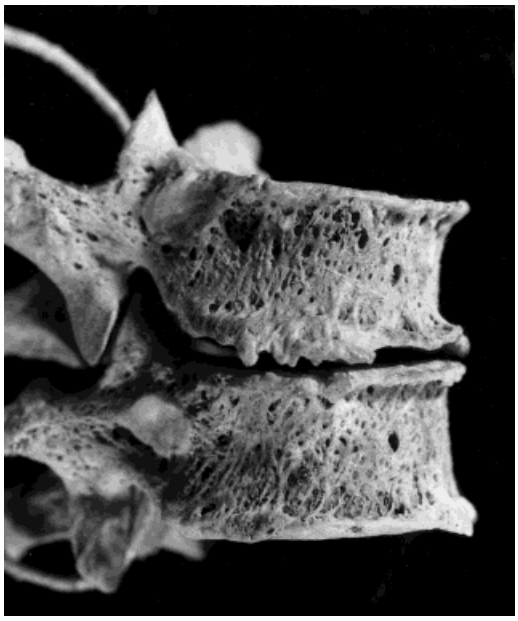

Fig. 16. Lateral view of thoracic vertebrae (HTH 2721). Holes and fronts of resorption.

The only disorders know to produce such mass effect lesions are gout, amyloidosis, sarcoidosis, and multicentric reticulohistiocytosis (Resnick and Niwayama, 1988). The latter has not been reported at this age. Bone involvement in sarcoidosis does occur at this age (Gershwin and Robbins, 1983), but cooccurrence of sarcoidosis and leukemia has not been reported (to our knowledge in children). Gout is a recognized complication of disorders associated with increased DNA release into the blood and hyperuricemia, such as childhood leukemia (Resnick and Niwayama, 1988). While systemic amyloidosis has been reported in young children with cystic fibrosis (as a complication of chronic infections) (McGlennen et al., 1986), we have not located a literature report of leukemia-related amyloidosis in children.

Can lymphocytic and myelocytic leukemia be distinguished? Is there a difference between adult and juvenile bone response to leukemia?

While there is more than one basis on which to categorize leukemia, one approach is to subdivide leukemias into myeloid and lymphatic cell line diseases. Both can be further divided into acute and chronic. The chronic varieties are paradoxically associated with minimal recognized bone involvement (Resnick and Niwayama, 1988), while bone involvement is almost universal in acute leukemia in children and reported in 43% of adults (Thomas et al., 1961). Eighty percent of acute leukemia in children is categorized as acute lymphocytic leukemia (Thomas et al., 1961; Gallagher et al., 1991), compared to 50% in adults. The frequency of bone involvement has been controversial. While Thomas et al. (1961) claimed that all children were affected, Rogalsky et al. (1986) and Silverstein and Kelly (1963) detected bone changes in only 75%. Silverstein and Kelly (1963) also reported bone changes in 385 of adults, indistinguishable (statistically) from the 43% reported by Thomas et al. (1961). Lest one consider childhood frequency (of radiologic bone lesions) different from that of adults, the Fisher exact test was 0.098 (not statistically significant). As Baty and Vogt (1965) reported transverse bands in 80% of acute myelogenous leukemia and 65% of acute lymphocytic leukemia, the radiologic picture may not allow distinguishing between the two varieties.

The character of lytic lesions showed little variation between these individuals with lymphocytic and myelocytic leukemia, with the exception of skeletal distribution and occurrence of crenulated lesions. Skeletal distribution differences are probably related to distribution of the leukemic cell generation in hematopoietic bone marrow. Hematopoietic marrow (contained in all bones at birth) is replaced in the extremities by the fifth to seventh year of life. This replacement continues, such that hemopoietic marrow in adults is limited to the axial skeleton and proximal protions of the extremities (Van Dyke et al., 1972; Williams, 1972).

Lytic lesions were more widely distributed in the individual with lymphocytic than they were in myelocytic leukemia. Periosteal reaction was more extensive in the skull and long bones of the individual with lymphocytic leukemia, while rib and vertebral involvement was limited to the individual with myelocytic leukemia.

It is unclear if the differences in the two individuals studied represent differences be-

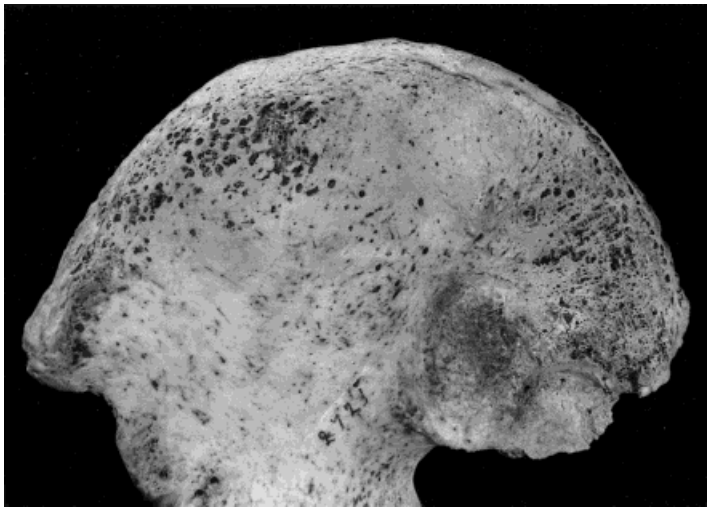

Fig. 17. Medial view of inominate (HTH 2721). Pitting (both holes and fronts of resorption). Superficial bone resorption along margins of superior iliac crest.

Fig. 18. Anterior-posterior x-ray view of inominate (HTH 2721). Solitary and coalescing lytic areas.

TABLE 3. Distribution (percent affected) of transverse bands in leukemia

Bone	Acute lymphocytic[1–3]	Acute myelocytic[3]
Humerus	55	0
Radius/ulna	65	8
Hands	8	0
Feet	25	0
Tibia/fibula	50	5
Femora	75	0
Inominate	85	2
Vertebrae	58	3

[1] Willson, 1959.
[2] Benz et al., 1976.
[3] Thomas et al., 1961.

tween myelocytic and lymphocytic leukemia or simply differences in susceptibility/responsiveness (Van Dyke et al., 1972; Williams, 1972) of adult and juvenile skeletons to leukemic insult. This aspect of the results must be considered tentative. The answer awaits availability of defleshed skeletons from additional affected individuals.

Differential diagnosis of forms of cancer in bone

The presence of lytic lesions in defleshed skeletons allows consideration of leukemia, but other hematologic malignancies, metastatic cancer, bone cell malignancy (e.g., osteosarcoma, Ewing sarcoma, multiple myeloma, lymphomatous disorders, histiocytosis, osteomyelitis, granulomatous infections [e.g., fungal, mycobacterial (such as tuberculosis), brucellosis], and even treponemal disease must also be considered (Resnick and Niwayama, 1988; Rothschild and Martin, 1993). The latter are typically associated with characteristic patterns of periosteal reaction, which should allow easy discrimination (Rothschild and Rothschild, 1995).

The lesions of leukemia can be distinguished from the filigree pattern of osteomyelitis (Rothschild and Martin, 1987) by the absence of the lace-like quality of the latter. The absence of disorganized trabeculae (characteristic of osteomyelitis) on macroscopic and radiologic examination in leukemia also facilitates distinguishing the disorders.

The size and general distribution of lesions in leukemia allow exclusion of such bone disorders/tumors as fibrous dysplasia, fibromas, simple and aneurysmal bone cysts, osteoblastomas, giant cell tumors, neuroblastoma, hemangiomas, angiosarcomas, lipomas, chondromas and enchondromas, chondroblastomas and chondrosarcomas, and amylodosis. The serpentine lesions of histiocytosis have not been observed in leukemia. Lacking macroscopic descriptions of lymphomatous bone disease (another white blood cell line tumor), we cannot assess contrasting lesions with leukemia.

Larger lesions, with extensive cortical disruption, and multilayered or sunburst periosteal reactions are signs of metastatic or bone cell malignancy, not of leukemia. Poorly demarcated lesions are more characteristic of malignant bone tumors and infections. Borders merging inperceptibly with the surrounding healthy bone are especially noted in Ewing sarcoma. The "punched out" lesions of multiple myeloma, eroding though adjacent structures, are easily distinguished from leukemic lesions.

CONCLUSIONS

Macroscopic skeletal changes, when present, appear sufficiently specific to allow distinguishing leukemia from other forms of cancer. While sample sizes this small require circumspection in their extrapolation to the general subject, the nature of leukemia lesions (in the two varieties of leukemia) appears unique and discernable from other sources of bone destruction. We have not observed this particular type of change in any skeleton (wherein the individual was known in life not to have had leukemia). This contrasts with radiologic findings, which appear less specific. It is unclear, however, that myelogenous and lymphocytic leukemia can be distinguished. While variation was noted, skeletons (studied to date) do not allow distinguishing between manifestations of the variety of leukemia and age-dependent bone susceptibility/responsiveness.

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